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(54) Title: DNA SEQUENCES ENCODING THE HUMAN A1, A2a and A2b ADENOSINE RECEPTORS			
(57) Abstract <p>The present invention relates to DNA sequences encoding the human A1, A2a and A2b adenosine receptors. In addition, the present invention relates to the use of these DNA sequences in the production of human A1, A2a and A2b adenosine receptors using recombinant DNA technology.</p>			

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DNA Sequences Encoding the Human A1, A2a and A2b
Adenosine Receptors

Field-of the Invention

The present invention relates to DNA sequences
5 encoding the human A1, A2a and A2b adenosine receptors.
In addition, the present invention relates to the use of
these DNA sequences in the production of the human A1, A2a
and A2b adenosine receptors using recombinant DNA
technology.

10 Background of the Invention

Adenosine influences cardiovascular function (by
slowing heart rate and decreasing blood pressure) and also
influences nervous system function (through sedative and
anti-epileptic effects). In addition, adenosine can
15 induce bronchoconstriction. Adenosine binds specifically
to at least three receptors, A1 and A2a and A2b.
Adenosine receptors have been shown to couple to a number
of second messenger systems. Additional adenosine
receptor subtypes may exist. As adenosine receptor
20 agonists and antagonists may have commercial value as
anti-hypertensive agents, hypnotics, anti-psychotics and
bronchodilators, the ability to produce adenosine
receptors by recombinant DNA technology is advantageous.

The present inventors have isolated three related
25 cDNA fragments encoding the human A1, A2a and A2b
adenosine receptors from human hippocampal cDNA by using
either the polymerase chain reaction and unique degenerate
oligonucleotides to generate specific probes or by using
specific consensus oligonucleotide probes for cDNA library
30 screening. Full-length cDNA clones for each of the three
receptors were isolated from a human hippocampal cDNA
library. The receptor sequences were identified as the
human A1, A2a and A2b adenosine receptors by expression in
mammalian cells and both measurement of the affinity of
35 the encoded receptors for various adenosine analogues and

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the effect of receptor activation on cAMP synthesis. The receptors have homology to cDNA's encoding the dog A1 and A2a adenosine receptors (MAENHAUT, C., VAN SANDE, J., LIBERT, F., ADRAMOWIC, M., PARMENTIER, M.,
5 VANDERHAEGEN, J., DUMONT, D., VASSART, G. AND SCHIFFMANN, S. (1990); LIBERT, F., SCHUFFMANN, S.M., LEFORT, A., PARMENTIER, M., GERARD, C., DUMONT, J.E., VANDERHAEGHEN J.J., VASSART, G. (1991)) and the rat A2b adenosine receptor (STEHLE, J.H., RIVKEES, S.A.,
10 LEE, J.J., WEAVER, D.R., DEEDS, J.D. AND REPPERT, S.M. (1992)). These hippocampal cDNA sequences represent novel human receptors which may be of clinical and commercial importance.

Summary of the Invention

15 Accordingly, in a first aspect the present invention consists in a DNA molecule encoding the human A1 adenosine receptor, the DNA molecule having a sequence substantially as shown in Figure 1 or a functionally equivalent sequence.

20 In a second aspect the present invention consists in a DNA molecule encoding the human A2a receptor subtype, the DNA molecule having a sequence substantially as shown in Figure 2 or a functionally equivalent sequence.

25 In a third aspect the present invention consists in a DNA molecule encoding the human A2b adenosine receptor subtype, the DNA molecule having a sequence substantially as shown in Figure 3 or a functionally equivalent sequence.

As used herein the term "functionally equivalent sequence" is intended to cover variations in the DNA sequence which, due to degeneracy of the DNA code, do not result in the sequence encoding a different polypeptide.
30 Further, this term is intended to cover alterations in the DNA code which lead to changes in the encoded polypeptide, but in which such changes do not affect the biological activity of the polypeptide.

35 As used herein the term "DNA molecule" is intended to

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cover both genomic DNA and cDNA.

In a fourth aspect the present invention consists in a method of producing the human A1 adenosine receptor comprising culturing a cell transformed with the DNA molecule of the first aspect of the present invention under conditions which allow expression of the DNA sequence such that the human A1 adenosine receptor is expressed on the cell surface and optionally recovering the human A1 adenosine receptor.

10 In a fifth aspect the present invention consists of a method of producing a human A2a adenosine receptor comprising culturing a cell transformed with the DNA molecule of the second aspect of the present invention under conditions which allow expression of the DNA sequence such that the human A2 adenosine receptor is expressed on the cell surface and optionally recovering the human A2a adenosine receptor.

15 In a sixth aspect the present invention consists of a method of producing a human A2b adenosine receptor comprising culturing a cell transformed with the DNA molecule of the third aspect of the present invention under conditions which allow expression of the DNA sequence such that the human A2 adenosine receptor is expressed on the cell surface and optionally recovering the human A2b adenosine receptor.

20 In further aspects the present invention consists of a method of screening a molecule for adenosine agonist or antagonist activity, comprising contacting the molecule with the human A1, A2a or A2b adenosine receptors produced by the method of the fourth, fifth or sixth aspect of the present invention.

25 In yet a further aspect the present invention consists in oligonucleotides 305, 377 and 376 as hereinafter described.

30 35 The DNA molecules of the present invention represent

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novel human receptors. These receptors may be of interest both clinically and commercially as they are expressed in many regions of the body and as adenosine affects a wide number of systems.

5 The isolated full-length DNA clones containing the complete coding region for these receptors can be used to establish mammalian cell lines producing the receptors for use in agonist and antagonist screening. The receptor DNA sequence can be used for additional homology screening to
10 identify novel members of this receptor family.

In order that the nature of the present invention may be more clearly understood preferred forms thereof will now be described with reference to the following examples and figures in which:-

15 Figure 1 shows the nucleotide and amino acid sequence of the human A1 adenosine receptor cDNA.

Figure 2 shows the nucleotide and amino acid sequence of the human A2a adenosine receptor cDNA.

20 Figure 3 shows the nucleotide and amino acid sequence of the human A2b adenosine receptor cDNA.

Figure 4A shows saturation isotherms of the total (unfilled triangle), specific (filled circle) and non-specific (unfilled square) binding of the A1 adenosine receptor antagonist DPCPX (8-cyclopentyl-1,3 dipropylxanthine) to mammalian CHO.K1 cells expressing the
25 human A1 adenosine receptor.

Figure 4B shows competition binding curves showing the displacement of CGS-21680 2-p-(2-Carboxyethyl)phenethylamino-5'-N-ethylcarboxyamido
30 adenosine hydrochloride) by different adenosine agonists and antagonists (NECA = 5'-N-ethylcarboxamido adenosine; CA=2-chloroadenosine; CPA=N⁶-cyclopentyladenosine; XAC=xanthine amine congener; T=8-(p-sulphophenyl)-theophylline) in mammalian HEK 293 cells expressing the
35 human A2a adenosine receptor.

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Figure 5 shows the effects of the different adenosine receptor subtypes, A₁, A_{2a} and A_{2b} upon cyclic AMP production. A₁ adenosine receptor activation leads to inhibition of forskolin stimulated cAMP levels.

- 5 Activation of both the A_{2a} and A_{2b} adenosine receptors (by CGS-21680 and NECA, respectively) leads to stimulation of cAMP levels.

METHODS

Oligonucleotide Design and Synthesis

- 10 Unique degenerate oligonucleotides corresponding to
the transmembrane II (TM II) and IV (TM IV) regions of G
protein-coupled receptors and containing either a 5' EcoRI
restriction enzyme site (TM II oligonucleotide 377) or a
3' Hind III restriction enzyme site (TM IV
15 oligonucleotides 305 and 376) were synthesized on an
Applied Biosystems automated DNA synthesiser. The
sequences of the oligonucleotides are as follows:-

305 5' - CCCAATAAGCTTAGICCIATGGCGAAAGACAGGGACCCA-3'

20 A A G G C
A A

376 5' - GAGTCCGAAGCTTAGTGGGCAAGAGATGGCGAAIGAIAGIACCA-3'

G TA C A G
T A

377 5' - CAGAACGAATTCAATGTTTATGGGTCTTTGTCITCIACTGA-3'

C G G G G G C A

The DNA sequences included inosine (I) residues. Crude oligonucleotides were then used in the polymerase chain reaction.

PCR Amplification

- ### 35 Sequences homologous to the G protein-coupled

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- receptor oligonucleotides were amplified from human cDNA using PCR and the Hybaid thermocycler. DNA was prepared from a human neuroblastoma (Clontech) cDNA library in lambda gt10 and from a hippocampal (Stratagene) cDNA
- 5 library in lambda ZapII. DNA was prepared by phenol and chloroform extraction of approximately 10^8 library phage and ethanol precipitation to recover the DNA. DNA from the cDNA libraries (1-5 μ g) was incubated with 200 μ M of each dNTP, 0.5 μ M oligonucleotide, 0.5 units Tth enzyme
- 10 (Toyobo) in 50mM KCl, 50mM Tris-HCl pH9.0, 1.5mM MgCl₂ (1 x PCR buffer) in a 50 μ L reaction volume. Samples were layered with 50 μ L light mineral oil (Sigma).
- Reactions were denatured for 5 minutes at 95°C. The PCR conditions were as follows: Denaturation for 2 minutes at
- 15 92°C, annealing for 2 minutes at 55°C, and extension for 2 minutes at 92°C, 2 minutes at 50°C, and 2 minutes at 70°C, repeated five times; then 2 minutes at 95°C, 2 minutes at 45°C, and 2 minutes at 70°C, repeated thirty times.
- 20 Subcloning and Sequencing of Amplified DNA Fragments
- Amplified DNA (20 μ l) was removed and analysed by gel electrophoresis in 1% agarose and 3% NuSieve (SeaKem). Amplification products 260bp-330bp in length were excised from the gel and purified with Geneclean.
- 25 DNA fragments were then digested with Hind III for one hour at 37°C and EcoRI for one hour at 37°C, the DNA again purified with Geneclean and eluted into 10 μ l H₂O. Digested DNA fragments were then subcloned into M13mp19 and sequenced by the Sanger dideoxy
- 30 chain-termination method using the Pharmacia or the Promega DNA sequencing kit. Sequencing reactions were analysed on a 6% acrylamide, 7M urea gel, dried onto Whatman 3M paper, and exposed to X-ray film for sixteen hours (Kodak X-OMAT AR5) at room temperature overnight.
- 35 Sequence Analysis of Novel DNA Sequences

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Sequence analysis of the DNA fragments generated from the PCR amplification identified two DNA fragments that had sequences common to other known G protein-coupled receptors. PCR amplification of neuroblastoma cDNA with 5 the degenerate oligonucleotides 377 and 305 produced a cDNA fragment which was designated 3.1. PCR amplification of human hippocampal cDNA with the degenerate oligonucleotides 377 and 376 produced a cDNA fragment with a sequence that was 76% homologous at the nucleotide level 10 to sequence 3.1 and was designated 3.2. The DNA sequences were searched on the GenBank and EMBL databases for comparison to known sequences and were confirmed to be novel sequences with a high level of homology to dog adenosine A1 and A2 receptors.

15 Isolation of Full-Length cDNA Clones

Full-length cDNA clones encoding the A1 receptor as well as receptor sequences corresponding to 3.1 and 3.2 were isolated from a human hippocampal cDNA library (Stratagene).

20 A1 adenosine receptor cDNA isolation

Specific consensus oligonucleotides corresponding to the second extracellular loop (679), and to the third intracellular loop (678) were synthesised on an Applied Biosystems automated DNA synthesiser. The sequences of 25 the oligonucleotides are as follows:-

678 5' - CCCGTAGTACTCTGCGGGTCGCCAGAGGGAGGCGACACCTTCTTGCC-3'

679 5' -GAGGCCAGCGGGCTGGCGGCCAACGGCAGCGGCAGCGAGCCC GTG-3'

30 Approximately 5×10^5 plaques were plated on C600 HflA bacterial cells. Plaques were lifted onto Hybond-N+nylon filters (0.45 μ M, 137mm, Amersham). DNA was denatured on the filters with a 3 minute incubation on 0.5 M NaOH, 1.5M NaCl and neutralised with a 5 minute 35 incubation in 0.5M Tris pH72, 1mM EDTA and 1.5M NaCl. DNA

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was fixed to the filters with a 15 minute exposure to 0.4M NaOH. Filters were then rinsed in 2 x SSC (3M NaCl, 0.3M sodium citrate) and allowed to dry before a 30 minute prehybridisation in 40% formamide, 5 x SSC, 5 x 5 Denhardt's, 50mM NaPO₄, 0.5% sodium dodecyl sulphate (SDS), 0.1mg/ml salmon sperm DNA at room temperature. Oligonucleotides 678 and 679 were pooled and 50 pmoles total were radiolabelled using γ^{32} P-ATP and the DNA 5' end-labelling system (Promega). The filters were 10 hybridised with this radiolabelled probe overnight at 42°C, after which time they were washed once briefly in 2 x SSC at room temperature then twice for 10 minutes each wash in 2 x SSC, 0.1% SDS at room temperature with a final wash in 0.1 x SSC, 0.1% SDS for 15 minutes at 50°C. The 15 filters were then exposed to Kodak X-OMAT AR5 film overnight at -70°C. Over twenty pure phage isolates which hybridised to the radiolabelled 678 and 679 oligonucleotides were obtained. Several of these different cDNAs were sequenced. The sequence of one such 20 cDNA (together with the deduced amino acid sequence) which encodes the human A1 adenosine receptor is shown in Figure 1.

A2a and A2b adenosine receptor cDNA isolation

Approximately 1 x 10⁶ plaques were plated on 25 C600HflA bacterial cells. Plaques were lifted onto Hybond-N nylon filters (0.45μM, 137mm, Amersham). DNA was denatured on the filters with a 3 minute incubation on 0.5M NaOH, 1.5M NaCl and neutralised with a 7 minute incubation in 0.5M Tris pH 7.2, 1mM EDTA and 1.5M NaCl. 30 Filters were rinsed in 2 x SSC (20 x SSC is 3M NaCl, 0.3M sodium citrate) and DNA fixed to the filters with a 5 minute exposure to ultraviolet light (312nm). Filters were prehybridised in 5 x SSPE (5 x SSPE=0.5M NaCl, 0.05M NaH₂PO₄, 0.0005M EDTA, pH 7.7), 5 x Denhardt's (0.1% 35 (w/v) bovine serum albumin, 0.1% (w/v) Ficoll, 0.1% (w/v)

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polyvinylpyrrolidone), 0.5% sodium dodecyl sulphate (SDS), 0.2mg/ml salmon sperm DNA at 65°C for 17 hours. The filters were hybridised with a radiolabelled probe corresponding to the PCR amplified DNA fragment encoding 5 the 300 bp of 3.1 (labelled with (α -³²P)-dCTP using the random primers DNA labelling system (Bethesda Research Laboratories)). Following hybridisation of the radiolabelled probe for 20 hours at 65°C, filters were washed with 2 x SSPE; 0.1% SDS at room temperature for 10 minutes, then with 1 x SSPE, 0.1% SDS at room temperature for 10 minutes and exposed to Kodak X-OMAT AR5 film for seven days at -70°C. Two pure phage isolates were hybridised to the radiolabelled 3.1 DNA fragment were obtained. The two DNA inserts were excised from the phage 15 vector using EcoRI digestion and subcloned into M13mp19 for sequencing. Sequence analysis indicated that one cDNA insert of approximately 2.6 kilobases encoded the full-length clone for the 3.2 receptor. The sequence of the cDNA (together with the putative amino acid sequence) 20 insert encoding the 3.1 receptor (the human A2a adenosine receptor) is shown in Figure 2 (together with the deduced amino acid sequence of the human A2a adenosine receptor) whilst the sequence of the cDNA insert encoding the 3.2 receptor (the human A2b adenosine receptor) is shown in 25 Figure 3 (together with the deduced amino acid sequence).

Expression of the cloned A1, A2a and A2b adenosine receptors in mammalian cells

Each cloned full-length cDNA was subcloned into a mammalian cell expression vector (pcDNA1neo for A2a and 30 A2b and pRc/CMV for A1 (Invitrogen)) in such a way as to direct expression of the encoded receptor portion.

Mammalian cell lines (Chinese Hamster Ovary - CHO K1 or Human Embryonic Kidney - HEK 293) were independently transfected with the recombinant expression vectors and 35 cell lines established which had stably integrated the

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cloned receptor DNA. The stably transfected cell lines were examined for their ability to bind a range of adenosine analogues as shown in Figure 4. Furthermore, the effect on cyclic AMP (cAMP) levels of receptor 5 activation by adenosine agonists was examined as shown in Figure 5.

These studies demonstrate that cDNA clone 3.1 encodes an adenosine A_{2a} receptor, cDNA clone 3.2 encodes an adenosine A_{2b} receptor and that the A₁ cDNA encodes an 10 adenosine A₁ receptor. Generation of significant amounts of purified receptor protein, made possible by this invention, can be used as a tool to facilitate the design and chemical synthesis of highly specific agonists and antagonists for each receptor subtype. Knowledge of the 15 primary sequence differences between the related receptor subtypes as determined by this invention provides crucial information for the design of receptor subtype specific agonists and antagonists.

It will be appreciated by persons skilled in the art 20 that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as 25 illustrative and not restrictive.

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CLAIMS:-

1. A DNA molecule encoding the human A₁ adenosine receptor, the DNA molecule having a sequence substantially as shown in Figure 1 or a functionally equivalent sequence.
- 5 2. A DNA molecule encoding the human A_{2a} receptor subtype, the DNA molecule having a sequence substantially as shown in Figure 2 or a functionally equivalent sequence.
3. A DNA molecule encoding the human A_{2b} adenosine receptor subtype, the DNA molecule having a sequence substantially as shown in Figure 3 or a functionally equivalent sequence.
- 10 4. A method of producing the human A₁ adenosine receptor comprising culturing a cell transformed with the DNA molecule as claimed in Claim 1 under conditions which allow expression of the DNA sequence such that the human A₁ adenosine receptor is expressed on the cell surface and optionally recovering the human A₁ adenosine receptor.
- 15 5. A method of producing a human A_{2a} adenosine receptor comprising culturing a cell transformed with the DNA molecule as claimed in Claim 2 under conditions which allow expression of the DNA sequence such that the human A_{2a} adenosine receptor is expressed on the cell surface and optionally recovering the human A_{2a} adenosine receptor.
- 20 6. A method of producing a human A_{2b} adenosine receptor comprising culturing a cell transformed with the DNA molecule as claimed in Claim 3 under conditions which allow expression of the DNA sequence such that the human A_{2b} adenosine receptor is expressed on the cell surface and optionally recovering the human A_{2b} adenosine receptor.
- 25 7. A method of screening a molecule for adenosine agonist or antagonist activity, comprising contacting the molecule with the human A₁, A_{2a} and A_{2b} adenosine receptors produced by the method as claimed in any one of Claims 3 to 6.

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Sequence Range: 1 to 1290

10	20	30	40	
CGC AGG ATG GTG CCT GCC TCG TGC CCC TTG GTG CCC GTC TGC TGA TGT				
50	60	70	80	90
GCC CAG CCT GTG CCC GCC ATG CCG CCC TCC ATC TCA GCT TTC CAG GCC				
Met Pro Pro Ser Ile Ser Ala Phe Gln Ala>				
100	110	120	130	140
GCC TAC ATC GGC ATC GAG GTG CTC ATC GCC CTG GTC TCT GTG CCC GGG				
Ala Tyr Ile Gly Ile Glu Val Leu Ile Ala Leu Val Ser Val Pro Gly>				
150	160	170	180	190
AAC GTG CTG GTG ATC TGG GCG GTG AAG GTG AAC CAG GCG CTG CGG GAT				
Asn Val Leu Val Ile Trp Ala Val Lys Val Asn Gln Ala Leu Arg Asp>				
200	210	220	230	240
GCC ACC TTC TGC TTC ATC GTC TCG CTG GCG GTG GCT GAT GTG GCC GTG				
Ala Thr Phe Cys Phe Ile Val Ser Leu Ala Val Ala Asp Val Ala Val>				
250	260	270	280	
GGT GCC CTG GTC ATC CCC CTC GCC ATC CTC ATC AAC ATT GGG CCA CAG				
Gly Ala Leu Val Ile Pro Leu Ala Ile Leu Ile Asn Ile Gly Pro Gln>				
290	300	310	320	330
ACC TAC TTC CAC ACC TGC CTC ATG GTT GCC TGT CGG GTC CTC ATC CTC				
Thr Tyr Phe His Thr Cys Leu Met Val Ala Cys Pro Val Leu Ile Leu>				
340	350	360	370	380
ACC CAG AGC TCC ATC CTG GGC CTG CTG GCA ATT GCT GTG GAC CGC TAC				
Thr Gln Ser Ser Ile Leu Ala Leu Leu Ala Ile Ala Val Asp Arg Tyr>				
390	400	410	420	430
CTC CGG GTC AAG ATC CCT CTC CCG TAC AAG ATG GTG GTG ACC CCC CGG				
Leu Arg Val Lys Ile Pro Leu Arg Tyr Lys Met Val Val Thr Pro Arg>				
440	450	460	470	480
AGG CGG CGG GTG GCC ATA GCC GGC TGC TGG ATC CTC TCC TTC GTG GTG				
Arg Ala Ala Val Ala Ile Ala Gly Cys Trp Ile Leu Ser Phe Val Val>				

FIG.1

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490	500	510	520	
GGA CTG ACC CCT ATG TTT GGC TGG AAC AAT CTG AGT CGG GTG GAG CGG Gly Leu Thr Pro Met Phe Gly Trp Asn Asn Leu Ser Ala Val Glu Arg>				
530	540	550	560	570
GCC TGG GCA GCC AAC GGC AGC ATG GGG GAG CCC GTG ATC AAG TGC GAG Ala Trp Ala Ala Asn Gly Ser Met Gly Glu Pro Val Ile Lys Cys Glu>				
580	590	600	610	620
TTC GAG AAG GTC ATC AGC ATG GAG TAC ATG GTC TAC TTC AAC TTC TTT Phe Glu Lys Val Ile Ser Met Glu Tyr Met Val Tyr Phe Asn Phe Phe>				
630	640	650	660	670
GTG TGG GTG CTG CCC CGC CTT CTC CTC ATG GTC CRC ATC TAC CTG GAG Val Trp Val Leu Pro Pro Leu Leu Leu Met Val Leu Ile Tyr Leu Glu>				
680	690	700	710	720
GTC TTC TAC CTA ATC CGC AAG CAG CTC AAC AAG AAG GTG TCG GCC TCC Val Phe Tyr Leu Ile Arg Lys Gln Leu Asn Lys Lys Val Ser Ala Ser>				
730	740	750	760	
TCC GGC GAC CCG CAG AAG TAC TAT GGG AAG GAG CTG AAG ATC GCC AAG Ser Gly Asp Pro Gln Lys Tyr Tyr Gly Lys Glu Leu Lys Ile Ala Lys>				
770	780	790	800	810
TCG CTG GCC CTC ATC CTC TTC CTC TTT GCC CTC AGC TGG CTG CCT TTG Ser Leu Ala Leu Ile Leu Phe Leu Phe Ala Leu Ser Trp Leu Pro Leu>				
820	830	840	850	860
CAC ATC CTC AAC TGC ATC ACC CTC TTC TGC CCG TCC TGC CAC AAG CCC His Ile Leu Asn Cys Ile Thr Leu Phe Cys Pro Ser Cys His Lys Pro>				
870	880	890	900	910
AGC ATC CTT ACC TAC ATT GCC ATC TTC CTC ACG CAC GGC AAC TCG GCC Ser Ile Leu Thr Tyr Ile Ala Ile Phe Leu Thr His Gly Asn Ser Ala>				

FIG.1 (cont'd.)

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920 *	930 *	940 *	950 *	960 *
ATG AAC CCC ATT GTC TAT GCC TTC CGC ATC CAG AAG TTC CGC GTC ACC Met Asn Pro Ile Val Tyr Ala Phe Arg Ile Gln Lys Phe Arg Val Thr>				
970 *	980 *	990 *	1000 *	
TTC CTT AAG ATT TGG AAT GAC CAT TTC CGC TGC CAG CCT GCA CCT CCC Phe Leu Lys Ile Trp Asn Asp His Phe Arg Cys Gln Pro Ala Pro Pro>				
1010 *	1020 *	1030 *	1040 *	1050 *
ATT GAC GAG GAT CTC CCA GAA GAG AGG CCT GAT GAC TAG ACC CCG CCT Ile Asp Glu Asp Leu Pro Glu Glu Arg Pro Asp Asp ***>				
1060 *	1070 *	1080 *	1090 *	1100 *
TCC GCT CCC ACC AGC CCA CAT CCA GTG GGG TCT CAG TCC AGT CCT CAC				
1110 *	1120 *	1130 *	1140 *	1150 *
ATG CCC GCT GTC CCA GGG GTC TCC CTG AGC CTG CCC CAG CTG GGC TGT				
1160 *	1170 *	1180 *	1190 *	1200 *
TGG CTG GGG GCA TGG GGG AGG CTC TGA AGA GAT ACC CAC AGA GTG TGG				
1210 *	1220 *	1230 *	1240 *	
TCC CTC CAC TAG GAG TTA ACT ACC CTA CAC CTC TGG GCC CTG CAG GAG				
1250 *	1260 *	1270 *	1280 *	1290 *
GCC TGG GAG GGA AGG GTC CTA CGG AGG GAC CAG CTG TCT AGA				

FIG.1 (cont'd.).

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Sequence Range: 1 to 2575

10	20	30	40	
*	*	*	*	
CAA TTT TCA GCT GTT CTT TGC TCA ATA ATA ACT TTT TTA TCA CCA AGA				
50	60	70	80	90
*	*	*	*	*
TAT CTC TCT AAG TTT TTG ACA TAT TCC TCA TTT GTT TTG ATA AAA GTT				
100	110	120	130	140
*	*	*	*	*
TTC TTA TTT TCT TAG AAA AAT AAG TTA CTA AAA GTC ATA TAT CAT TGT				
150	160	170	180	190
*	*	*	*	*
ATA TCT TCA AAA TAT TGC TTA AAA CTA GGA CCT GTA TTT AAA TGT TTT				
200	210	220	230	240
*	*	*	*	*
TTC TTC TTA AAG ACA ATT TGC AGG TGC CCT CAG GAA CCC TGA AGC TGG				
250	260	270	280	
*	*	*	*	
GCT GAG CCA TGA TGC TGC CAG AAC CCC TGC AGA GGG CCT GGT TTC				
290	300	310	320	330
*	*	*	*	*
AGG AGA CTC AGA GTC CTC TGT GAA AAA GCC CTT GGA GAG CGC CCC AGC				
340	350	360	370	380
*	*	*	*	*
AGG GCT GCA CTT GGC TCC TGT GAG GAA GGG GCT CAG GGG TCT GGG CCC				
390	400	410	420	430
*	*	*	*	*
CTC CGC CTG GGC CGG GCT GGG AGC CAG GCG GGC GGC TGG GCT GCA GCA				
440	450	460	470	480
*	*	*	*	*
AAT GGA CCG TGA GCT GGC CCA GCC CGC GTC CGT GCT GAG CCT GCC TGT				
490	500	510	520	530
*	*	*	*	*
CGT CTG TGG CC ATG CCC ATC ATG GGC TCC TCG GTG TAC ATC ACG GTG GAG Met Pro Ile Met Gly Ser Ser Val Tyr Ile Thr Val Glu>				
540	550	560	570	
*	*	*	*	
CTG GCC ATT GCT GTG CTG GCC ATC CTG GGC AAT GTG CTG GTG TGC TGG Leu Ala Ile Ala Val Leu Ala Ile Leu Gly Asn Val Leu Val Cys Trp>				

FIG. 2

SUBSTITUTE SHEET

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580	590	600	610	620
*	*	*	*	*
GCC GTG TGG CTC AAC AGC AAC CTG CAG AAC GTC ACC AAC TAC TTT GTG Ala Val Trp Leu Asn Ser Asn Leu Gln Asn Val Thr Asn Tyr Phe Val>				
630	640	650	660	670
*	*	*	*	*
GTG TCA CTG GCG GCG GCC GAC ATC GCA GTG GGT GTG CTC GCC ATC CCC Val Ser Leu Ala Ala Asp Ile Ala Val Gly Val Leu Ala Ile Pro>				
680	690	700	710	720
*	*	*	*	*
TTT GCC ATC ACC ATC AGC ACC GGG TTC TGC GCT GCC TGC CAC GGC TGC Phe Ala Ile Thr Ile Ser Thr Gly Phe Cys Ala Ala Cys His Gly Cys>				
730	740	750	760	770
*	*	*	*	*
CTC TTC ATT GCC TGC TTC GTC CTG GTC CTC ACG CAG AGC TCC ATC TTC Leu Phe Ile Ala Cys Phe Val Leu Val Leu Thr Gln Ser Ser Ile Phe>				
780	790	800	810	
*	*	*	*	
AGT CTC CTG GCC ATC GCC ATT GAC CGC TAC ATT GCC ATC CGC ATC CCG Ser Leu Leu Ala Ile Ala Ile Asp Arg Tyr Ile Ala Ile Arg Ile Pro>				
820	830	840	850	860
*	*	*	*	*
CTC CGG TAC ATT GGC TTG GTG ACC GGC ACG AGG GCT AAG GGC ATC ATT Leu Arg Tyr Asn Gly Leu Val Thr Gly Thr Arg Ala Lys Gly Ile Ile>				
870	880	890	900	910
*	*	*	*	*
GCC ATC TGC TGG GTG CTG TCG TTT GCC ATC GGC CTG ACT CCC ATG CTA Ala Ile Cys Trp Val Leu Ser Phe Ala Ile Gly Leu Thr Pro Met Leu>				
920	930	940	950	960
*	*	*	*	*
GGT TGG AAC AAC TGC GGT CAG CCA AAG GAG GGC AAG AAC CAC TCC CAG Gly Trp Asn Asn Cys Gly Gln Pro Lys Glu Gly Lys Asn His Ser Gln>				
970	980	990	1000	1010
*	*	*	*	*
GGC TGC GGG GAG GGC CAA GTG GCC TGT CTC TTT GAG GAT GTG GTC CCC Gly Cys Gly Glu Gly Gln Val Ala Cys Leu Phe Glu Asp Val Val Pro>				
1020	1030	1040	1050	
*	*	*	*	
ATG AAC TAC ATG GTG TAC TTC AAC TTC TTT GCC TGT GTG CTG GTG CCC Met Asn Tyr Met Val Tyr Phe Asn Phe Phe Ala Cys Val Leu Val Pro>				
1060	1070	1080	1090	1100
*	*	*	*	*
CTG CTG CTC ATG CTG GGT GTC TAT TTG CGG ATC TTC CTG GCG GCG CGA Leu Leu Leu Met Leu Gly Val Tyr Leu Arg Ile Phe Leu Ala Ala Arg>				
1110	1120	1130	1140	1150
*	*	*	*	*
CGA CAG CTG AAG CAG ATG GAG AGC CAG CCT CTG CCG GGG GAG CGG GCA Arg Gln Leu Lys Gln Met Glu Ser Gln Pro Leu Pro Gly Glu Arg Ala>				

FIG. 2 (cont'd.)

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1160 1170 1180 1190 1200
 * * * * *
 CCG TCC ACA CTG CAG AAG GAG GTC CAT GCT GCC AAG TCA CTG GCC ATC
 Arg Ser Thr Leu Gln Lys Glu Val His Ala Ala Lys Ser Leu Ala Ile>

 1210 1220 1230 1240 1250
 * * * * *
 ATT GTT GGG CTC TTT GCC CTC TGC TGG CTC CCC CTA CAC ATC ATC AAC
 Ile Val Gly Leu Phe Ala Leu Cys Trp Leu Pro Leu His Ile Ile Asn>

 1260 1270 1280 1290 1300
 * * * * *
 TGC TTC ACT TTC TGC CCC GAC TGC ACC CAC GCC CCT CTC TGG CTC
 Cys Phe Thr Phe Phe Cys Pro Asp Cys Ser His Ala Pro Leu Trp Leu>

 1310 1320 1330 1340 1350
 * * * * *
 ATG TAC CTG GCC ATC GTC CTC TCC CAC ACC AAT TCG GTC GTG AAT CCC
 Met Tyr Leu Ala Ile Val Leu Ser His Thr Asn Ser Val Val Asn Pro>

 1360 1370 1380 1390 1400
 * * * * *
 TTC ATC TAC GCC TAC CGT ATC CGC GAG TTC CGC CAG ACC TTC CGC AAG
 Phe Ile Tyr Ala Tyr Arg Ile Arg Glu Phe Arg Gln Thr Phe Arg Lys>

 1410 1420 1430 1440 1450
 * * * * *
 ATC ATT CGC AGC CAC GTC CTG AGG CAG CAA GAA CCT TTC AAG GCA GCT
 Ile Ile Arg Ser His Val Leu Arg Gln Gln Glu Pro Phe Lys Ala Ala>

 1460 1470 1480 1490 1500
 * * * * *
 GGC ACC AGT GCC CGG GTC TTG GCA GCT CAT GGC AGT GTC GGA GAG CAG
 Gly Thr Ser Ala Arg Val Leu Ala Ala His Gly Ser Val Gly Glu Gln>

 1510 1520 1530 1540 1550
 * * * * *
 GTC AGC CTC CGT CTC AAC GGC CAC CCG CCA GAG GTG TGG GCC AAC GGC
 Val Ser Leu Arg Leu Asn Gly His Pro Pro Glu Val Trp Ala Asn Gly>

 1560 1570 1580 1590 1600
 * * * * *
 AGT GCT CCC CAC CCT GAG CGG AGG CCC AAT GGC TAC GCC CTG GGG CTG
 Ser Ala Pro His Pro Glu Arg Arg Pro Asn Gly Tyr Ala Leu Gly Leu>

 1610 1620 1630 1640 1650
 * * * * *
 GTG AGT GGA GGG AGT GCC CAA GAG TCC CAG GGG AAC ACG GGC CTC CCA
 Val Ser Gly Gly Ser Ala Gln Glu Ser Gln Gly Asn Thr Gly Leu Pro>

 1660 1670 1680 1690 1700
 * * * * *
 GAC GTG GAG CTC CTT AGC CAT GAG CTC AAG AGA GTG TGC CCA GAG CCC
 Asp Val Glu Leu Leu Ser His Glu Leu Lys Arg Val Cys Pro Glu Pro>

 1710 1720 1730 1740 1750
 * * * * *
 CCT GGC CTC GAT GAC CCC CTG GCC CAG GAT GGA GCA GGA GTG TCC TGA
 Pro Gly Leu Asp Asp Pro Leu Ala Gln Asp Gly Ala Gly Val Ser ***>

 1760 1770 1780 1790 1800
 * * * * *
 TGA TTC ATG GAG TTT GCC CCT TCC TAA G GGA AGG AGA TCT TTA TCT TTC
 *** Phe Met Glu Phe Ala Pro Ser ***>

FIG. 2 (cont'd.)

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1780	1790	1800	1810	1820											
*	*	*	*	*											
TGG	TTC	GCT	TGA	CCA	GTC	ACG	TTC	GGA	GAA	GAG	AAG	GAG	TGC	CAG	GAG
1830	1840	1850	1860	1870											
*	*	*	*	*											
ACC	CTG	AGG	GCA	GCC	GGT	TCC	TAC	TTT	GGA	CTG	AGA	GAA	GGG	AGC	CCC
1880	1890	1900	1910	1920											
*	*	*	*	*											
AGG	CTG	GAG	CAG	CAT	GAG	GCC	CAG	CAA	GAA	GGG	CIT	GGG	TTC	TGA	GGA
1930	1940	1950	1960	1970											
*	*	*	*	*											
AGC	AGA	TGT	TTC	ATG	CTG	TGA	GGC	CIT	GCA	CCA	GGT	GGG	GGC	CAC	AGC
1980	1990	2000	2010												
*	*	*	*												
ACC	AGC	AGC	ATC	TTT	GCT	GGG	CAG	GCC	CCA	GCC	CTC	CAC	TGC	AGA	AGC
2020	2030	2040	2050	2060											
*	*	*	*	*											
ATC	TGG	AAG	CAC	CAC	CIT	GTC	TCC	ACA	GAG	CAG	CIT	GGG	CAC	AGC	AGA
2070	2080	2090	2100	2110											
*	*	*	*	*											
CTG	GCC	TGG	CCC	TGA	GAC	TGG	GGA	GTG	GCT	CCA	ACA	GCC	TCC	TGC	CAC
2120	2130	2140	2150	2160											
*	*	*	*	*											
CCA	CAC	ACC	ACT	CTC	CCT	AGA	CTC	TCC	TAG	GGT	TCA	GGA	GCT	GCT	GGG
2170	2180	2190	2200	2210											
*	*	*	*	*											
CCC	AGA	GGT	GAC	ATT	TGA	CIT	TTT	TTC	CAG	GAA	AAA	TGT	AAG	TGT	GAG
2220	2230	2240	2250												
*	*	*	*												
GAA	ACC	CIT	TTT	ATT	TTA	TTA	CCT	TTC	ACT	CTC	TGG	CTG	CTG	GGT	CTG
2260	2270	2280	2290	2300											
*	*	*	*	*											
CCG	TGG	GTC	CTG	CTG	CTA	ACC	TGG	CAC	CAG	AGC	CTC	TCC	CCC	GGG	AGC
2310	2320	2330	2340	2350											
*	*	*	*	*											
CTC	AGG	CAG	TCC	TCT	CCT	GCT	GTC	ACA	GCT	GCC	ATC	CAC	TTC	TCA	GTC
2360	2370	2380	2390	2400											
*	*	*	*	*											
CCA	GGG	CCA	TCT	CIT	GGA	GIG	ACA	AAG	CTG	GGA	TCA	AGG	ACA	GGG	AGT
2410	2420	2430	2440	2450											
*	*	*	*	*											
TGT	AAC	AGA	GCA	GIG	CCA	GAG	CAT	GGG	CCC	AGG	TCC	CAG	GGG	AGA	GGT
2460	2470	2480	2490												
*	*	*	*												
TGG	GGC	TGG	CAG	GCC	ACT	GGC	ATG	TGC	TGA	GTA	GCG	CAG	AGC	TAC	CCA
2500	2510	2520	2530	2540											
*	*	*	*	*											
GIG	AGA	GGC	CIT	GTC	TTA	CTG	CCT	TTC	CIT	CTA	AAG	GGA	ATG	TTT	TTT
2550	2560	2570													
*	*	*													
TCT	GAG	ATA	AAA	TTA	AAA	CGA	GCC	ACA	G						

FIG.2 (cont'd.)

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Sequence Range: 1 to 1687

10	20	30	40	
*TC AGC CCC GAG GCT CAG AAG CGG CAG GCG GAG GCG CGG TCC GGG CGC				
60	70	80	90	
*TAT GGC CAT GCC CGG CGG GTC TCA CGC GGC TGC CCC TCG CCC GGC GCG				
100	110	120	130	140
*CCT TCG GTA GGG GGC GCC CGG GGC CCA GCT GGC CGG GCC ATG CTG CTG				
Met Leu Leu>				
150	160	170	180	190
*GAG ACA CAG GAC GCG CTG TAC GTG GCG CTG GAG CTG GTC ATC GCC GCG				
Glu Thr Gln Asp Ala Leu Tyr Val Ala Leu Glu Leu Val Ile Ala Ala>				
200	210	220	230	240
*CTT TCG GTG GCG GGC AAC GTG CTG GTG TGC GCC GCG GTG GGC ACG GCG				
Leu Ser Val Ala Gly Asn Val Leu Val Cys Ala Ala Val Gly Thr Ala>				
250	260	270	280	
*AAC ACT CTG CAG ACG CCC ACC AAC TAC TTC CTG GTG TCC CTG GCT GCG				
Asn Thr Leu Gln Thr Pro Thr Asn Tyr Phe Leu Val Ser Leu Ala Ala>				
290	300	310	320	330
*GCC GAC GTG GCC GTG GGG CTC TTC GCC ATC CCC TTT GCC ATC ACC ACC				
Ala Asp Val Ala Val Gly Leu Phe Ala Ile Pro Phe Ala Ile Thr Ile>				
340	350	360	370	380
*AGC CTG GGC TTC TGC ACT GAC TTC TAC GGC TGC CTC TTC CTC GCC TGC				
Ser Leu Gly Phe Cys Thr Asp Phe Tyr Gly Cys Leu Phe Leu Ala Cys>				
390	400	410	420	430
*TTC GTG CTG GTG CTC ACG CAG AGC TCC ATC TTC AGC CTT CTG GCC GTG				
Phe Val Leu Val Leu Thr Gln Ser Ser Ile Phe Ser Leu Leu Ala Val>				
440	450	460	470	480
*GCA GTC GAC AGA TAC CTG GCC ATC TGT GTC CCG CTC AGG TAT AAA AGT				
Ala Val Asp Arg Tyr Leu Ala Ile Cys Val Pro Leu Arg Tyr Lys Ser>				
490	500	510	520	
*TTG GTC ACG GGG ACC CGA GCA AGA GGG GTC ATT GCT GTC CTC TGG GTC				
Leu Val Thr Gly Thr Arg Ala Arg Gly Val Ile Ala Val Leu Trp Val>				

FIG. 3

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530	540	550	560	570
*	*	*	*	*
CTT GCC TTT GGC ATC GGA TTG ACT CCA TTC CTG GGG TGG AAC AGT AAA Leu Ala Phe Gly Ile Gly Leu Thr Pro Phe Leu Gly Trp Asn Ser Lys>				
580	590	600	610	620
*	*	*	*	*
GAC AGT GCC ACC AAC AAC TGC ACA GAA CCC TGG GAT GGA ACC ACG AAT Asp Ser Ala Thr Asn Asn Cys Thr Glu Pro Trp Asp Gly Thr Thr Asn>				
630	640	650	660	670
*	*	*	*	*
GAA AGC TGC TGC CCT GTG AAG TGT CTC TTT GAG AAT GTG GTC CCC ATG Glu Ser Cys Cys Leu Val Lys Cys Leu Phe Glu Asn Val Val Pro Met>				
680	690	700	710	720
*	*	*	*	*
AGC TAC ATG GTA TAT TTC AAT TTC TTT GGG TGT GTR CTG CCC CCA CTG Ser Tyr Met Val Tyr Phe Asn Phe Phe Gly Cys Val Leu Pro Pro Leu>				
730	740	750	760	
*	*	*	*	
CTT ATA ATG CTG GTG ATC TAC ATT AAG ATC TTC CTG GTG GCC TGC AGG Leu Ile Met Leu Val Ile Tyr Ile Lys Ile Phe Leu Val Ala Cys Arg>				
770	780	790	800	810
*	*	*	*	*
CAG CTT CAG CGC ACT GAG CTG ATG GAC CAC TCG AGG ACC ACC CTC CAG Gln Leu Gln Arg Thr Glu Leu Met Asp His Ser Arg Thr Thr Leu Gln>				
820	830	840	850	860
*	*	*	*	*
CGG GAG ATC CAT GCA GCC AAG TCA CTG GCC ATG ATT GTG GGG ATT TTT Arg Glu Ile His Ala Ala Lys Ser Leu Ala Met Ile Val Gly Ile Phe>				
870	880	890	900	910
*	*	*	*	*
GCC CTG TGC TGG TTA CCT GTG CAT GCT GTT AAC TGT GTC ACT CCT TTC Ala Leu Cys Trp Leu Pro Val His Ala Val Asn Cys Val Thr Leu Phe>				
920	930	940	950	960
*	*	*	*	*
CAG CCA GCT CAG GGT AAA AAT AAG CCC AAG TGG GCA ATG AAT ATG GCC Gln Pro Ala Gln Gly Lys Asn Lys Pro Lys Trp Ala Met Asn Met Ala>				
970	980	990	1000	
*	*	*	*	
ATT CCT CTG TCA CAT GCC AAT TCA GTR GTC AAT CCC ATT GTC TAT GCT Ile Leu Leu Ser His Ala Asn Ser Val Val Asn Pro Ile Val Tyr Ala>				
1010	1020	1030	1040	1050
*	*	*	*	*
TAC CGG AAC CGA GAC TTC CGC TAC ACT TTT CAC AAA ATT ATC TCC AGG Tyr Arg Asn Arg Asp Phe Arg Tyr Thr Phe His Lys Ile Ile Ser Arg>				
1060	1070	1080	1090	1100
*	*	*	*	*
TAT CCT CTC TGC CAA GCA GAT GTC AAG AGT GGG AAT GGT CAG GCT GGG Tyr Leu Leu Cys Gln Ala Asp Val Lys Ser Gly Asn Gly Gln Ala Gly>				

FIG.3 (cont'd.)

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1110 1120 1130 1140 1150
 * * * * *
 GTC CAG CCT GCT CTC GGT GTC GGC CTA TGA TCT AGG CTC TCG CCT CTT
 Val Gln Pro Ala Leu Gly Val Gly Leu ***>

 1160 1170 1180 1190 1200
 * * * * *
 CCA GGA GAA GAT ACA AAT CCA CAA GAA ACA AAG AGG ACA CGG CTG GTT

 1210 1220 1230 1240
 * * * *
 TTC ATT GTG AAA GAT AGC TAC ACC TCA CAA GGA AAT GGA CTG CCT CTC

 1250 1260 1270 1280 1290
 * * * * *
 TTG AGC ACT TCC CTG GAG CTA CCA CGT ATC TAG CTA ATA TGT ATG TGT

 1300 1310 1320 1330 1340
 * * * * *

 CAG TAG TAG CAC CAA GGA TTG ACA AAT ATA TTT ATG ATC TAT TCA GCT

 1350 1360 1370 1380 1390
 * * * * *
 GCT TTT ACT GTG TGG ATT ATG CCA ACA GCT TGA ATG GAT TCT AAC AGA

 1400 1410 1420 1430 1440
 * * * * *
 CTC TTT TGT TTT TAA AAG TCT GCC TTG TTT ATG GTG GAA AAT TAC TGA

 1450 1460 1470 1480
 * * * *
 AAC TAT TTT ACT GTG AAA CAG TGT GAA CTC TTA TAA TGC AAA TAC TTT

 1490 1500 1510 1520 1530
 * * * * *
 TTA ACT TAG AGG CAA TGG AAA AAT AAA AGT TGA CTG TAC TAA AAA TGT

 1540 1550 1560 1570 1580
 * * * * *
 ATA CTT GTT GCC AGG AAG GTG ACC TCA AAA ATT AAA AGT ATA ATT ATT

 1590 1600 1610 1620 1630
 * * * * *
 CGG CCG GGC ATG GTG GCT CAC ACC TGT AAT TCC AGC ACT TTG GGA GGC

 1640 1650 1660 1670 1680
 * * * * *
 CAA GGC AGG CGG ATC ACG AGG TCA GGA GTT CAA AAC CAG CCT GTC CAA

 TAT AGT G

FIG.3 (cont'd.)

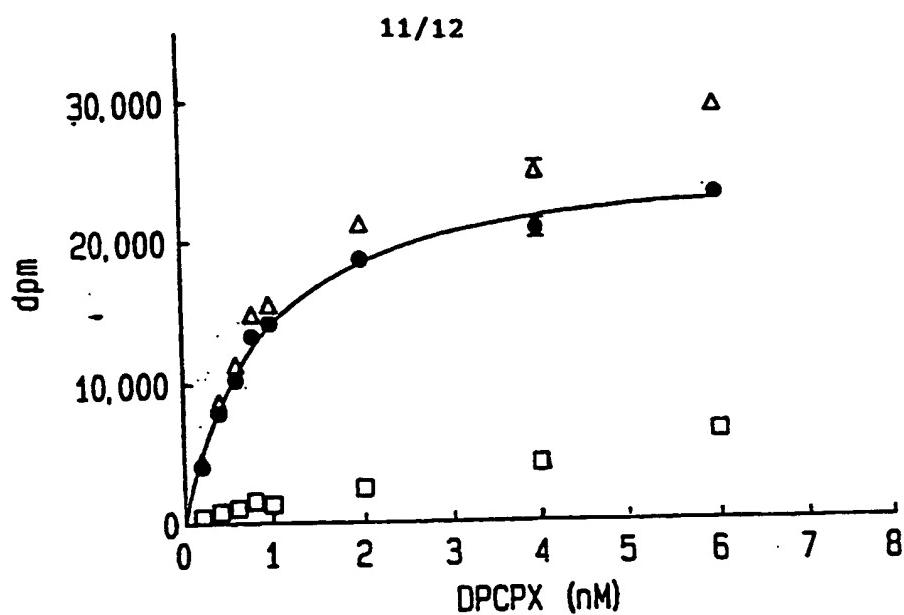


FIG. 4a

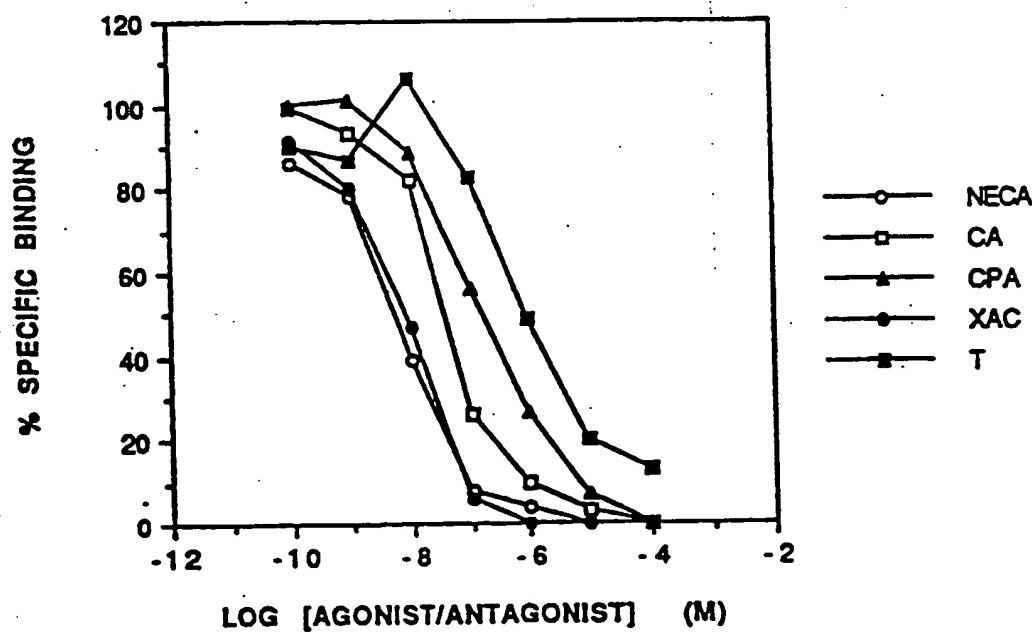


FIG. 4b

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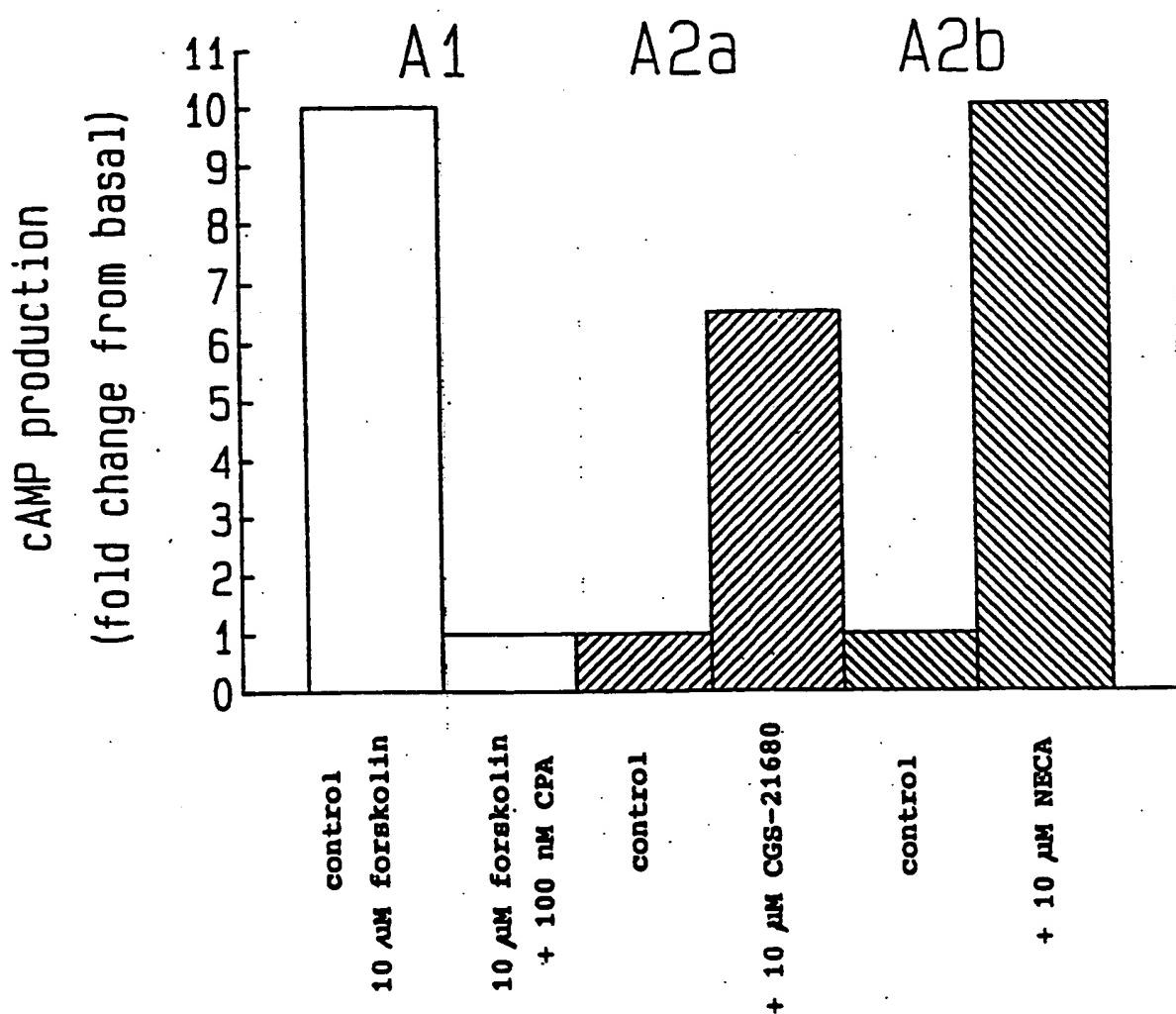


FIG. 5

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00277A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.⁵ C12N 15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC⁵: C12N 15/12Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC C12N 15/12Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
Derwent Database: WPAT - Keywords Adenosin: ADE, Receptor, C12N
BIOT - Keywords Adenosin: ADE, Receptor
CASA - Keywords Adenosin: ADE, Receptor, DNA or Gene, A1, A2A or A2B

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	AU,A,21791/92 (THE UNITED STATES OF AMERICA REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 10 December 1992 (10.12.92)	1-7
Y	AU,A,75792/91 (THE UNITED STATES OF AMERICA REPRESENTED BY THE SECRETARY, U.S. DEPARTMENT OF COMMERCE) 31 October 1991 (31.10.91)	1-7
Y	GENOMICS 11,225-227 (1991) CHROMOSOMAL MAPPING OF A1 & A2 ADENOSINE RECEPTORS, VIP RECEPTOR, & A NEW SUBTYPE OF SEROTONIN RECEPTOR, Published 1991	1-7

 Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search 26 August 1993 (26.08.93)	Date of mailing of the international search report 2 SEP 1993 (2.09.93)
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA	Authorized officer  JOHN ASHMAN
Faximile No. (06) 2832364	Telephone No. (06) 2832364

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00277

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
A	AU,A,52215/90 (MERRELL DOW PHARMACEUTICALS INC) 4 October 1990 (04.10.90)	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 93/00277

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
WO 92/21701	AU 21791/92
WO 91/16056	AU 75792/91
END OF ANNEX	

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